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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,710	04/08/2004	Michael Wayne Graham	546322000304	1697

20872 7590 06/29/2005
MORRISON & FOERSTER LLP
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EXAMINER

SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/821,710

Applicant(s)

GRAHAM ET AL.

Examiner

Daniel M. Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44 and 47-61 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44 and 47-61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/25/05, 2/11/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a reply to the Paper filed 29 April 2005 in response to the Non-Final Office action mailed 11 February 2005. Claims 62-76 were withdrawn from consideration and claims 44-61 were considered in the 11 February Office Action. Claims 45, 46 and 62-76 were canceled and claim 44 was amended in the 29 April Paper. Claims 44 and 47-61 are currently pending and under consideration.

Priority

In the previous Office Action, the claims were denied benefit of the parent application because the parent applications contain no support for an RNA sequence limited to about 20-100 nucleotides in length. The Office Action asserts that the closest teaching is found in the second full paragraph on page 8 of the instant application and states, “[n]ormally, a sequence of greater than 20-100 nucleotides should be used, though a sequence of greater than about 200-300 nucleotides would be preferred...”, which teaching is the same as the teachings found in the priority documents. The Office Action asserts that the skilled artisan would not have viewed this statement as teaching that the nucleic acid of the invention should be limited to between about 20-100 nucleotides. In contrast, the statement teaches away from the limitation, actually indicating that the nucleic acids of the invention should be greater than this range. Thus, the skilled artisan would not have viewed the parent applications as providing descriptive support for the invention as claimed in the instant application. Therefore, the instant application is considered a continuation-in-part of the parent applications and the claims are afforded an effective filing date of 8 April 2004.

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In response, Applicant has amended claim 44 to recite that the first RNA sequence is greater than 20-100 nucleotides in length. Although this generic recitation finds descriptive support in the priority applications, the species recited in claims 49-57 are not disclosed in the parent applications and, as described herein above, the parent applications actually teach away from species less than 100 base pairs in length. Therefore, the limitations of claims 49-57 are not adequately described in the parent applications and the instant application is properly a continuation-in-part of the parent applications.

Information Disclosure Statement

The information disclosure statement filed 29 April 2005 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Specifically, the Examiner can find no PTO/SB/17 in the 29 April submission.

Oath/Declaration

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The oath or declaration **stands objected to** as defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration was objected to because the application was filed with a copy of the declaration executed in the parent and does not reflect the status of the application as a continuation-in-part.

In response, Applicant contends that the amendments to the claims remove the subject matter identified as new matter and, therefore, the application is properly a continuation of the parent application. However, as described herein above, the application still contains subject matter that was not disclosed in the parent application and is therefore a continuation-in-part. Furthermore, even if all of the unsupported subject matter were removed from the claims, the application, as filed, is a continuation-in-part and will remain a continuation-in-part throughout prosecution.

Specification

Objection to the abstract is **withdrawn** in view of the filing of a substitute abstract.

Objection to the specification as disclosing sequence data without an accompanying "SEQ ID NO:" referring to the sequence listing is **withdrawn** in view of the amendments to the specification.

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The specification **stands objected to** as failing to provide proper antecedent basis for the claimed subject matter. The specification still does not provide antecedent basis for the size limitations set forth in claims 49-55. The specification should be amended to recite these limitations as stated in the originally filed claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44 and 47-61 **stand rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising a first RNA sequence wherein said first RNA sequence is about 20-100 nucleotides in length and a second RNA sequence wherein said second RNA sequence is complementary to said first RNA sequence, wherein the first nucleic acid molecule is identical to a sequence complementary to a region of a target gene known at the time of filing to be capable of effecting post-transcriptional repression, delay or otherwise reduction of a target gene in a mammalian cell, does not reasonably provide enablement for the broad scope of any isolated nucleic acid molecule capable of post-transcriptionally repressing, delaying or otherwise reducing expression of a target gene in a mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In response to the *prima facie* case of record, Applicant has amended claim 44 to recite that the first RNA sequence is identical to a sequence complementary to a region of a target gene. Applicant contends that the Examiner has accepted that the specification is enabling for an isolated nucleic acid molecule that is identical to a sequence complementary to a region of a target gene. However, this assertion is clearly not consistent with the statement of the rejection set forth in the previous Office Action and reiterated herein above. In particular, the Office Action states that the specification is enabling for an isolated nucleic acid molecule comprising a first RNA sequence wherein said first RNA sequence is about 20-100 nucleotides in length and wherein the first nucleic acid molecule is identical to a sequence complementary to a region of a target gene known at the time of filing to be capable of effecting post-transcriptional repression, delay or otherwise reduction of a target gene in a mammalian cell. The amendments and arguments do not address these aspects of the rejection. In fact, the amendment to claim 44 expands the scope of the claim such that it is now directed to RNA sequences “greater than about 20-100 nucleotides in length”. Thus, the claim is now encompasses any nucleic acid greater than 20 nucleotides in length.

The art teaches that obtaining specific RNAi in a mammalian cell using RNA molecules greater than about 30 nucleotides in length is highly unpredictable. For example, Lin *et al.* US Pub No. 2004/0106566 teaches (paragraph 0004; emphasis added, citations omitted),

Although PTGS/RNAi phenomena appear to offer a potential avenue for inhibiting gene expression, their applications have not been demonstrated to work constantly in higher vertebrates and, therefore, the widespread use thereof in higher vertebrates is still questionable. For example, the findings of RNAi effects are based on the transfection use of double-stranded RNA (dsRNA), which have shown to cause interferon-induced non-specific RNA degradation in mammalian cells []. Such an interferon-induced cellular response usually reduces the specificity of RNAi-associated gene silencing effects and may cause a severe cytotoxic side-effect to the transfected cells []. Especially in

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mammalian cells, it has been noted that the gene silencing effects of dsRNA-mediated RNAi phenomena are repressed by the interferon-induced global RNA degradation when the dsRNA size is larger than 25 base-pairs (bp).

Likewise, Verma *et al.* US Pub No. 2004/0234504 teaches, “[i]n most mammalian cells dsRNA provokes a non-specific cytotoxic response. In contrast, the introduction of siRNAs, as provided by the present invention, appears to suppress gene expression without producing a non-specific cytotoxic response because the small size of the siRNAs, as compared to dsDNA, prevents activation of the dsRNA-inducible interferon system in mammalian cells and avoids the non-specific phenotypes that can be observed by introducing larger dsRNA” (paragraph 0034; emphasis added).

Thus, the art clearly recognizes that obtaining sequence-specific degradation of an RNA transcript of a target gene by an endogenous system of the mammalian cell becomes more unpredictable as the size of the inhibitory RNA molecule is increased. Therefore, claims 44-48 and 58-61 are clearly not enabled over their full scope.

With regard to claims 49-57, Applicant’s response does not address the unpredictability of obtaining an RNAi response using an siRNA targeted to any given region of any given gene (see the first and second paragraphs on page 9 and page 11 of the previous Office Action).

Applicant’s arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §112, first paragraph as lacking an enabling disclosure.

Claim Rejections - 35 USC § 102

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44 and 47-61 **stand** rejected under 35 U.S.C. 102(a) as being anticipated by Harborth *et al.* (publicly available 12 May 2003) *Antisense Nucl. Acid Drug Devel.* 13:83-105 for reasons of record and herein below in the response to amendment and arguments.

Claims 44, 47, 54 and 56-61 **stand** rejected under 35 U.S.C. 102(b) as being anticipated by McManus *et al.* (2002) *RNA* 8:842-850 for reasons of record and herein below in the response to amendment and arguments.

Claims 44, 47, 49-53, 56, 57, 60 and 61 **stand** rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir *et al.* (2002) *Methods* 26:199-213 (made of record in the IDS filed 2 August 2004) for reasons of record and herein below in the response to amendment and arguments.

Response to Amendment and Arguments

In response to the art rejections of record, Applicant has amended claim 44 such that it is now directed to an isolated nucleic acid comprising a first RNA sequence greater than 20-100 nucleotides in length. Applicant contends that cited art does not anticipate the claims because the

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claims are entitled to the priority date of the earliest parent application. However, this is clearly not the case for claims 49-57, which, as discussed above, recite size limitations that were not contemplated in the parent applications and from which the parent applications actually teach away. With regard to claims 44, 47, 48 and 58-61, although the limitations of the claims are described, Applicant's response failed to overcome the enablement rejection against the claims. As the disclosure of the parent applications is no more enabling than the disclosure of the instant application, the supporting disclosure of the parent applications still fails to meet with the requirements of 35 USC §112, first paragraph, and the claims are therefore not entitled to an earlier priority date.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected as anticipated by the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44, 47, 48 and 58-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is indefinite in reciting the size limitation "greater than 20-100 nucleotides in length". The supporting disclosure in the second full paragraph on page 8 states, "[n]ormally, a sequence of greater than 20-100 nucleotides should be used, though a sequence of greater than about 200-300 nucleotides would be preferred..." Thus, the specification appears to teach that

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nucleic acids within the range of 20-100 nucleotides should not be used in the method and limitation "greater than 20-100" should be viewed as greater than the entire range (*i.e.*, greater than 100). Alternatively, the limitation might be read as encompassing greater than 20 to less than 100 nucleotides in length, which is consistent with the limitations of claims 49-57. Given that claim might be interpreted in ways that appear to be mutually exclusive, the metes and bounds of the claimed subject matter is unclear.

In view of the context of the limitation as recited in the specification and consonant with the broadest reasonable interpretation of the claims, the limitation is construed as encompassing any nucleic acid greater than 20 nucleotides in length.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779.

The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636


DAVID GUZO
PRIMARY EXAMINER